REMARKS

Claims 1-13 are pending in the application. Claims 11-13 were previously presented in amended form. Claim 1 is currently amended. Claims 2-10 are original. A copy of the claims now pending in the application showing changes made to currently amended claims in accord with 37 CFR 1.121, as revised, has been provided.

No new matter has been introduced by virtue of the amendments made herein. Accordingly, Applicant respectfully requests their entry. In view of the amendments made herein and the remarks below, Applicant respectfully requests reconsideration and withdrawal of rejections set forth in the November 16, 2004 final action.

Rejection under 35 USC § 103(a)

In his final rejection the Examiner maintained his rejection of claims 1-13 under 35 USC § 103(a) as " being unpatentable over Doogan, et al (U.S. 4,962,128) in view of Howard, et al (U.S. 5,597,826) ... for the reason of the record on 8/10/04". The Examiner also withdrew the Johnson reference (EP0768083) from the rejection.

Without prejudice and in the interests of facilitating prosecution applicants have amended claim 1 by insertion of the term "solution" so that amended claim 1 recites "...an essentially nonaqueous, liquid concentrate solution ...". Support for this amendment is found in the "Detailed Description" section at page 6, line 23.

In the first point the Examiner asserts "...Doogan et al does teach the composition contains sertraline or its pharmaceutically acceptable salt, flavoring agents, and diluents, such as ethanol, glycerin and various like combinations thereof; also, the secondary Howard et al reference to supplement the primary reference does disclose that liquid preparations containing sertraline may be prepared by conventional means with pharmaceutically acceptable additives such as non-aqueous vehicles (see col. 22, lines 47-55)."

Applicants respectfully submit that the above cited Doogan reference teaches diluents such as ethanol and glycerin within "...aqueous suspensions and/or elixirs ..." Applicants respectfully refer the Examiner to Dorland's Illustrated Medical Dictionary, 25th edition, (publ. W. B. Saunders) where on page 125 the definition of the term "aqueous" is given as "watery; prepared with water." Applicants further respectfully note that those skilled in the art will recognize that the term "aqueous" is used to describe a liquid preparation, wherein the liquid in the preparation is primarily water. Further it is clear to those skilled in the art that Doogan's recital at col. 2, line 63 of "When aqueous suspensions and/or elixirs are desired for oral administration ...." describes aqueous preparations. Therefore Doogan's recital of "...flavoring agents, coloring matter...", "emulsifying and/or suspending agents, together with diluents..." is within the context of diluents used with a liquid preparation wherein the liquid is primarily water and the resulting preparation is an emulsion or a suspension, not a solution as recited by instant claim 1.

The Examiner has invoked Howard, which teaches pharmaceutical formulations with two active ingredients, as a secondary reference thus implicitly conceding that Doogan by itself neither teaches nor suggests the pharmaceutical composition of instant claim 1. The Examiner cites col. 22, lines 47-55 of the Howard reference which beginning at col. 22, line 47 and continuing to line 57, recites:

"Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid)."

Applicants respectfully submit that the Examiner has relied on teachings in Howard that do not refer to pharmaceutical preparations in which the sole active ingredient is sertraline, or a pharmaceutically acceptable sertraline salt, but rather compositions containing (a) 5-HT reuptake inhibitors, of which sertraline is a preferred species, and (b) an unspecified compound from the genus of compounds represented by Howard's formula I. The applicants respectfully refer the Examiner to the abstract, col. 1, line 6 - to col. 24, line 58 of the specification, and the claims, especially claim 1 at col. 64, lines 49 - 55). There is no suggestion in Howard that the compound of Howard's formula I is absent from or is to be removed from any preparation recited therein. Applicants submit the presence of another complex chemical species in Howard's pharmaceutical composition is a disincentive to the skilled artisan seeking guidance in the preparation of "an essentially nonaqueous, liquid concentrate solution ... comprising an amount of sertraline or a pharmaceutically acceptable salt thereof..." as it is unclear if Howard's teachings apply in the absence of compounds of Howard's formula I.

Applicants further submit that there is no indication in Howard that any of the means taught therein will produce "an essentially nonaqueous, liquid concentrate solution for oral administration comprising an amount of sertraline or a pharmaceutically acceptable salt thereof and one or more essentially nonaqueous pharmaceutically acceptable excipients" as recited in amended claim 1. Applicants respectfully refer the Examiner to the definition of the term "concentrate" at page 6, line 3 of the instant specification (second paragraph of the "Detailed Description" section which recites ""Concentrate" when used herein refers to a strong solution provided for dilution before use. (Butterworths Medical Dictionary, 2nd edition, Butterworths, London - Boston 1978, pp. 399-400.)"

Applicants further submit that Howard recites "...non-aqueous *vehicles* (e.g. almond oil, oily esters or ethyl alcohol)..." but the term vehicles, especially within the context of a formulation having two active ingredients, may refer to a medium in which these ingredients are suspended

rather than dissolved. There is no recital in Howard that the "non-aqueous vehicles" specifically form a solution with sertraline alone or with pharmaceutically acceptable salts of sertraline alone as opposed to an emulsion or suspension, and there is certainly no recital of a concentrate solution, let alone the "nonaqueous liquid concentrate solution" of claim 1.

The Examiner further states "it is well-known in the art that many liquid preparations of conventional means with pharmaceutically acceptable additives are available depending on the customer's choice." Applicants respectfully submit that the Examiner errs if the Examiner is indicating that the availability of liquid pharmaceutical preparations in general, make obvious the invention of a specific liquid pharmaceutical concentrate preparation designed to meet specific needs. Applicant respectfully submits that until a product based on the instant invention emerged no liquid concentrate solution of sertraline or a pharmaceutically acceptable salt thereof was available on the market. The Examiner concludes: "Therefore, if the skillful artisan ... had desired to develop the product containing non-aqueous liquid concentrate compositions of sertraline, it would have been obvious for the skillful artisan in the art to have [been] motivated to incorporate Howard et al's non-aqueous vehicles into the Doogan et al method because, for oral administration, Howard et al does indicate that non-aqueous vehicles can be incorporated in the liquid preparations containing sertraline."

Applicants further submit that Doogan's diluents and any combination thereof are in the context of "*aqueous* suspensions and/or elixirs." There is no recital in Doogan that specifically suggests that a "solution" let alone a "concentrate solution" and especially "an essentially nonaqueous, liquid concentrate solution" of sertraline or a pharmaceutically acceptable salt thereof can be achieved. The method of Doogan involves the use of water. The fact that Doogan teaches the use of water in all of the liquid preparations recited therein is in itself a disincentive to the skilled artisan seeking "an essentially nonaqueous, liquid concentrate solution..." There is therefore no motivation for the skilled artisan to rely on the teachings of Doogan in the search for "an essentially nonaqueous liquid concentrate solution". Even if the step were taken of using Howard's non-aqueous vehicles in the absence of Howard's compounds of formula I the skilled artisan would expect that combining Howard's non-aqueous vehicles with Doogan's teachings would result in an aqueous emulsion or suspension not a concentrate solution. There is no teaching in either of the cited references either separately or combined in the manner suggested by the Examiner that suggests or hints at the pharmaceutical composition of claim 1 which is not merely a liquid preparation but an "essentially nonaqueous, liquid concentrate solution ... comprising an amount of sertraline or a pharmaceutically acceptable salt thereof and one or more essentially nonaqueous pharmaceutically acceptable excipients..." Applicants respectfully submit, that there is no motivation, indeed there is a disincentive to combine Howard with Doogan.

In the second point the Examiner states Doogan teaches "that it is administered in dosages ranging from 50 - 500 mg/day." Applicant submits that the stated dosage level gives no

indication of the concentration of sertraline or a pharmaceutically acceptable salt thereof attainable within any specific non-aqueous solvent system or what that solvent system should be. The aforesaid dosage refers only to oral or parenteral administration (see col 2, line 18) and "can be carried out in both single and multiple dosages" (see col. 2, lines 29 - 30) and may employ any one of the many dosage forms listed at col. 2, lines 35 - 37, such as tablets. Applicant submits "...an essentially nonaqueous, liquid concentrate solution ..." as recited in currently amended claim 1 is not among these dosage forms.

The Examiner also states that Doogan discloses at col. 2, lines 45 -46 that "the composition contains sertraline with concentration levels ranging from 0.5% to 90% by weight of the total compositions ... or its pharmaceutically acceptable salt, flavoring agents, and diluents such as ethanol, propylene glycol, and glycerin (see from col. 2 line 65 to col. 3, line 2)." Applicants submit that the composition referred to at col. 2, lines 45 -46 may be any one of the many dosage forms listed at col. 2, lines 35 - 37, such as tablets. Applicants submit there is no reference to any "essentially nonaqueous, liquid concentrate solution ...." or to the concentration of sertraline or a pharmaceutically acceptable salt thereof that can be dissolved to form such a concentrate solution. Applicants submit that the diluents at col. 2 line 65 to col. 3, line 2 are directed to "*aqueous* suspensions and/or elixirs" (see col. 2, lines 63 - 64) and do not suggest or hint at the "essentially *non-aqueous* liquid concentrate solution" of claim 1.

The Examiner cites Howard as teaching "the dose of 0.3 mg to 10 mg per kg of body weight per day of the sertraline", at col. 23, lines 33 - 34. Applicants respectfully question the relevance of this teaching to the instant claims. Applicants submit that (a) any pharmaceutical preparation will be directed to delivering an effective dose of the medication contained therein, as this is the purpose of a pharmaceutical preparation, (b) the recital of dose levels for sertraline in Howard does not teach or suggest the quantities of sertraline or a pharmaceutically acceptable salt thereof that may be dissolved in an "essentially nonaqueous, liquid concentrate solution" as instantly claimed and (c) the dosage range cited by the Examiner is for a 5-HT reuptake inhibitor that is preferably sertraline *administered in combination* with "preferably ... 0.1 mg to about 3 mg. per kg. of body weight per day of a compound of formula I ..." (see col. 23, lines 25 - 40, especially lines 36 - 38): therefore this dose level may not apply when Howard's compound of formula I is absent as in the instant invention. The Examiner states "...it would have been obvious for the skillful artisan ... to have [been] motivated to incorporate Howard et al's non-aqueous vehicles into the Doogan et al method, thereby ascertaining the claimed dose by routine experimentation."

Applicants submit that because Howard has tailored his teachings to a pharmaceutical preparation containing a 5-HT reuptake inhibitor, that may preferably be sertraline, plus another active ingredient selected from a genus of compounds represented by Howard's formula I, the

skilled artisan would not be motivated to combine Howard with Doogan, indeed the constant presence of another active ingredient would be a disincentive to such a combination.

Applicants further respectfully submit that the Examiner has confused the term "dose" with the quantity of material dissolved in the concentrate solution of instant claim 1. At any given sertraline or sertraline salt concentration, the dose delivered will depend on the volume of solution delivered. Amended claim 1 recites "an essentially nonaqueous, liquid concentrate solution ... comprising an amount of sertraline or a pharmaceutically acceptable salt thereof" not doses. The instant invention provides a concentrated solution of sertraline or a pharmaceutically acceptable salt thereof so that an appropriate dose may be contained in a small volume of said solution, which as recited in the specification, can be dispersed in a relatively large volume of a beverage. Applicant submits that disclosure of the dosages of sertraline that may be administered in any of many dosage forms such as tablets is not the disclosure of the solubility of sertraline or its salts in a non-aqueous solvent or a combination of non-aqueous solvents.

As discussed above, applicants submit that even if Howard were combined with Doogan in the manner suggested by the Examiner, the essentially nonaqueous concentrate solution of currently amended claim 1 would not be produced. Indeed the Examiner concedes in the statement "...thereby ascertaining the claimed dose by routine experimentation." that the mere combination of Howard with Doogan is not enough to produce the concentrate solution of claim 1 since further experimentation would be required. Applicants submit that currently amended claim 1 is therefore unobvious over the cited references under 35 USC 103a. Applicants further submit that the Examiner's concession that "routine experimentation" would be required after combination of Howard with Doogan in the manner suggested by the Examiner, does not render the instant invention as recited in amended claim 1 unpatentable under 35 USC 103a, which recites "Patentability shall not be negatived by the manner in which the invention was made."

In the third point the Examiner has withdrawn the Johnson reference.

In his fourth point The Examiner states: "However there is a motivation to combine the references. Doogan, et al does disclose the pharmaceutical composition containing sertraline hydrochloride (see col. 1, line 68) with a dose from 25 mg to 200 mg for treating anxiety-related disorders (see col. 2, lines 20 -23);" Applicants submit that Doogan at col. 1, line 68, lists examples of "pharmaceutically acceptable salts of sertraline that can be used to treat anxiety-related disorders" but does not disclose a pharmaceutical composition. Applicants further submit that Doogan recites at col. 2, lines 16 - 21, "Sertraline or a pharmaceutically acceptable salt thereof, when used to treat anxiety-related disorders, may be administered either orally or parenterally. It is generally administered in dosages ranging from 50 - 500 mg per day when used to treat obsessive compulsive disorder, and from about 25-500 mg per day when used to treat other anxiety-related disorders," Applicants respectfully submit that the Examiner has confused the term dosage with the concentration of sertraline or a pharmaceutically acceptable salt in solution. The Examiner

refers to Doogan col. 2, line 65 to col. 3, line 2 as listing diluents. The diluents listed also include water and the diluents refer to "aqueous suspensions and/or elixirs" (col. 2, lines 63-64) but not an "essentially nonaqueous, liquid concentrate solution" as recited in amended claim 1. Applicants submit that the stated dosage range gives no indication of the concentration of sertraline or a pharmaceutically acceptable salt that is attainable within a specific non-aqueous solvent system or what that solvent system should be. The aforesaid dosage refers only to oral or parenteral administration (see col 2, line 18) and "can be carried out in both single and multiple dosages" (see col. 2, lines 29 - 30) and may employ any one of the many dosage forms listed at col. 2, lines 35 - 37, such as tablets. Applicant submits "...an essentially nonaqueous, liquid concentrate solution for oral administration..." as recited in claim 1 is not among these dosage forms.

The Examiner states "Howard et al discloses expressly the pharmaceutical composition containing sertraline hydrochloride (see col. 20, line 31) with a dose of from 0.1 mg to 200 mg (see col. 24, lines 7-8), ...non-aqueous vehicles such as ethyl alcohol...." Applicants submit that while Howard at col. 20, line 31 refers to sertraline hydrochloride the reference to sertraline hydrochloride at Howard, col. 24, lines 7-8, is in error as the doses recited therein refer to the genus of compounds of formula I (see col. 24, line 3). Applicants further submit that contrary to the Examiner's assertion, sertraline hydrochloride itself is never "expressly" disclosed in any of the pharmaceutical compositions described in Howard.

The Examiner asserts that Howard indicates at col. 20, lines 60-61 that pharmacologically acceptable anions for sertraline include methanesulfonate. Applicants respectfully submit that the Examiner errs. The aforesaid reference is to salts of the base compounds of Howard's formula I, not to sertraline.

Applicants further submit that Howard at col. 20, lines 63 - 66 refers to "Those compounds of the formula I which are also acidic in nature ... are capable of forming base salts with various pharmacologically acceptable cations." Applicants submit that such compounds of formula I due to the basic nature of sertraline or the cationic nature of a sertraline salt can interact with sertraline or a sertraline salt with the possible formation of insoluble residues. Applicants submit that Howard has tailored his teachings to a pharmaceutical preparation that always contains (a) a 5-HT reuptake inhibitor, preferably sertraline, or a salt thereof, and (b) another compound selected from the genus of compounds represented by Howard's formula I which can interact with sertraline or a salt thereof. Applicants submit that the skilled artisan would not be motivated to combine Howard with Doogan, since the constant presence of another active ingredient that can cause complications and the lack of teachings specifically related to sertraline and pharmaceutically acceptable salts thereof would be a disincentive to such a combination.

The Examiner refers to col. 22, lines 51 -56, of Howard which discloses components that may be used in compositions containing the aforementioned two active components. Instant

amended claim 1 recites a "an essentially nonaqueous, liquid concentrate solution ... comprising an amount of sertraline or a pharmaceutically acceptable salt thereof and one or more essentially nonaqueous pharmaceutically acceptable excipients; wherein at least one of the excipients is liquid.". Consequently, Howard's teaching of suspending agents is irrelevant and the teaching of non-aqueous "vehicles" such as ethyl alcohol does not disclose whether the vehicle produces a suspension, a solution or a combination of suspension and solution and does not teach or suggest a concentrate solution as recited in instant claim 1. There is no specific teaching in Howard of a composition whose only active ingredient is sertraline hydrochloride or any other pharmaceutically acceptable sertraline salt. Applicants submit the Examiner's reference to Howard's teaching of methanesulfonate salt is not relevant as this refers to Howard's compounds of formula I and not to sertraline itself.

The Examiner appears to assert that both Doogan and Howard definitively deal with pharmaceutical compositions containing "sertraline hydrochloride". Applicants submit that contrary to this, Doogan does not specifically refer to sertraline hydrochloride in connection with any liquid preparation and Howard never specifically refers to sertraline hydrochloride in connection with any preparation. Furthermore, the Examiner confuses "dose" with the concentration of an ingredient in solution. Contrary to the assertion of the Examiner, neither reference specifically refers to sertraline hydrochloride in a liquid preparation, let alone a nonaqueous solution concentrate.

The Examiner describes the skillful artisan as being motivated to combine Howard's methanesulfonate "into the Doogan et al pharmaceutical composition containing sertraline hydrochloride ...." Applicants respectfully submit there is no motivation whatsoever for this combination as Howard refers to methanesulfonate only with regard to the genus of compounds of formula I, and Doogan never specifically recites sertraline hydrochloride in any liquid preparation.

Applicants further submit that even if the references were to be combined in the manner described by the Examiner, the Examiner concedes that even after such combination the skilled artisan would need to perform "routine experimentations" "to achieve the non-aqueous liquid concentrate having the unique amounts and combination of excipients ...." Applicants respectfully submit that the Examiner has conceded that the amounts and combination of excipients of the non-aqueous liquid concentrate of instant claims 1-13 are "unique" and cannot be arrived at without further "routine experimentation". Applicants submit that the Examiner has conceded that the concentrate solution of instant claim 1 is therefore unobvious over the references combined in the manner suggested by the Examiner, as the amounts and composition are "unique" and must be arrived at by "routine experimentation". Applicants submit that 35 USC 103a, recites "Patentability shall not be negatived by the manner in which the invention was made." Applicants request allowance of instant currently amended claim 1 and claims 2-13 since

even if the manner by which the "unique" composition of instant claim 1 was achieved was "routine experimentation" it is patentable under 35 USC 103a.

Applicants further respectfully submit that a non-aqueous sertraline hydrochloride concentrate solution based on the instant claims is currently being sold to meet the needs of patients who are non-compliant with treatment because they "...dislike or have difficulty swallowing tablets or capsules..." (see page 3 line 24 - page 4, line 2 of the instant specification). The applicants submit that the instant invention provides a technical solution to this problem in the form of the instant nonaqueous oral concentrate solution which permits the dispersal of the appropriate dose, contained in a very small volume of concentrate solution, in a large volume of a beverage having an acceptable taste. (See page 8, line 30 - page 9, line 7 of the instant specification.). Applicants submit that the commercial product based on the instant claims meets a long-felt need and that the instant claims are therefore patentable under 35 USC 103(a) and respectfully request withdrawal of the rejection and allowance of these claims.

For all of the foregoing reasons applicants submit that instant claim 1, as currently amended, is patentable under 35 USC 103(a) over the cited references, either separately or in the combination cited by the Examiner, and respectfully request withdrawal of the rejection. Applicants further submit that claims 2-13 all of which incorporate the novel and unobvious features of claim 1, are all patentable under 35 USC § 103(a) over the cited references, either separately or in the combination cited by the Examiner, and respectfully request withdrawal of the rejection.

In view of the amendments set forth herein and remarks above, the applicant respectfully submits that the pending claims are fully allowable, and solicits the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicant's undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

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